

Remarks

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Thus, claim 1 has been amended to change "comprises", in connection with the recitation of the drug layer, to "consists essentially of", the significance of which will be discussed below in connection with the patentability arguments.

Claims 7 and 8 have been added to the application. New claim 7 is the same as amended claim 1 except that it defines the drug layer in "consists of" language instead of "consists essentially of" language. Claim 8 combines amended claims 1 and 6 but further defines the softening agent and absorption promoting agent based on the disclosures at page 7, lines 7-8 and 17 of the specification.

The patentability of the presently claimed invention after entry of the foregoing amendments, over the disclosures of the references relied upon by the Examiner in rejecting the claims, will be apparent upon consideration of the following remarks.

Thus, the rejection of claims 1, 4 and 6 under 35 U.S.C. §103(a) as being unpatentable over Kim et al. (WO '276) in view of Brantl et al. (US '686) and further in view of McQuinn (US '860) is respectfully traversed.

(A) The subject matter of newly amended claim 1 of the present application is a patch containing fentanyl for the mucous membrane of the oral cavity, which comprises a drug layer, a support layer hardly soluble or insoluble in water comprising ethyl cellulose and hydroxypropyl methylcellulose, on the drug layer, and a backing on the support layer, wherein the drug layer **consists essentially of** fentanyl or its salt as an active ingredient, methyl vinyl ether-maleic anhydride copolymer as an adhesive agent, and at least one substance selected from HPC, HPMC and HEC as a thickener.

According to the present invention this patch:

- (1) does not need any complex procedures when it is applied,
- (2) gives little uncomfortable feeling in the oral cavity,
- (3) can quickly increase the serum concentration as the drug is absorbed almost at the applied region,
- (4) makes less transfer of the drug into the gastrointestinal tract by preventing the drug release into other parts of the oral cavity except the applied region,

- (5) is easily torn off when it becomes unnecessary,
- (6) can easily control the serum concentration of the drug,
- (7) is usable as a rescue preparation for pangs during therapy for cancer pain, and
- (8) is highly safe.

The present inventors found that a drug layer which **consists essentially of** fentanyl or its salt as an active ingredient, methyl vinyl ether-maleic anhydride copolymer as an adhesive (e.g. 5 to 90 wt/%), and at least one substance selected from the group consisting of hydroxypropyl methylcellulose, hydroxypropyl methylcellulose and hydroxyethyl cellulose as a thickener (e.g. 0.2 to 80 wt/%) shows sufficient adhesivity to the mucous membrane of the oral cavity due to the presence of water, easily releases the drug from the applied surface, and quickly increases the serum concentration of the drug.

Furthermore, by laminating a support layer which is insoluble or hardly soluble in water comprising ethyl cellulose and hydroxypropyl methylcellulose on the opposite side of the adhesive surface of the drug layer, the drug is hardly swallowed with saliva due to protecting against release of the drug into other regions of the oral cavity except the applied region. In addition, by equipping a backing layer thereto and making the patch thick to some extent, regardless of smallness of the size, handling of the patch (such as picking up, applying and tearing off) becomes easy. A patch containing fentanyl for the mucous membrane of the oral cavity which can easily control the serum concentration of the drug can thus be obtained.

The excellent effect of the present invention is shown in Tests 1 to 4 and Figures 2 to 5 of the present application.

(B) The Kim et al. reference relates to a transdermal drug delivery composition comprising a hydrophilic polymer base, a drug, a lipophilic permeation enhancer and a compatibilizer consisting essentially of an **acrylate polymer** which compatibilizes the lipophilic enhancer with the hydrophilic polymer base and which renders the composition thermodynamically stable (see claim 1.).

As a problem to be solved, Kim et al. describe that a technique of preparing a **uniform, stable** hydrogel composition for transdermal drug delivery, which includes **both a hydrophilic component**, i.e. a hydrophilic polymer base, and **lipophilic substances**, i.e. permeation enhancers, is needed (see page 3, lines 26 to 29).

As a means for solving the above problem, the reference describes that the invention is based on the discovery that a stable hydrogel composition can be formulated for transdermal delivery of drugs, wherein an **acrylate polymer** is used as a compatibilizer which compatibilizes the lipophilic component, i.e. the enhancer, with the hydrophilic polymer base and which renders a uniform composition which is **thermodynamically stable** (see page 8, lines 20-24).

The hydrogel composition of Kim et al. comprises, for example, the following ingredients:

- (1) a hydrophilic polymer base (such as PVP, PVA, maleic anhydride/vinyl ether copolymer, etc.),
- (2) a drug,
- (3) a lipophilic permeation enhancer such as a saturated fatty acid, an unsaturated fatty acid, an ester thereof, etc.,
- (4) a compatibilizer consisting of an acrylate polymer such as acrylic acid polymer, methacrylic acid polymer, alkyl acrylate polymer, alkyl methacrylate polymer, copolymer thereof, etc., and
- (5) water as a solvent (see page 8, last line to page 9, line 10).

As mentioned above, and as described in Kim et al., the hydrogel composition contains a hydrophilic compound, a lipophilic compound and further a compatibilizer which is an **acrylate polymer** in order to compatibilize both compounds as essential ingredients, as well as an active drug.

(C) On the other hand, the drug layer of the patch of the present invention **consists essentially of** ethyl vinyl ether maleic anhydride copolymer as an adhesive agent, and HPC, HPMC, and/or HEC as a thickener, in addition to the drug. An **acrylate polymer**, required by Kim et al., is not contained therein.

According to Kim et al., as mentioned above, by compatibilizing both a hydrophilic substance and a lipophilic substance using an acrylate polymer, the desired effect, namely a stable and uniform hydrogel would be attained. There is no suggestion in this reference which would lead one of ordinary skill in the art to omit the acrylate polymer from the composition, since to do so would prevent achieving this desired effect, which is an object of the Kim et al. reference.

Furthermore, Kim et al. never disclose such a support layer as in the present invention, but only disclose a usual backing layer (see page 15, line 30 to page 16, line 10, referring to an impenetrable base such as a plastic sheet like polyethylene, nylon, a nonwoven fabric, etc).

Therefore, it is clear that the subject matter of claims 1, 4 and 6 of the present application are patentably distinct from the subject matter disclosed in Kim et al.

(D) Brantl et al. describe that a support layer may be provided between the reservoir layer and the backing layer (see column 4, lines 13 to 17). But the support layer consists of a laminate of a thin aluminum foil and a polyethylene film. Such a support layer is different from the one used in the present invention.

(E) McQuinn relates to a method of measuring the blood level of a drug in a mammal by adhering a device such as a patch which is free of a drug to a mucosal surface of the mammal. Therefore, the present invention is completely different from McQuinn in the problem to be solved.

In addition the backing layer is not illustrated therein.

(F) As mentioned above with respect to Kim et al., the subject matter of this reference is very different from the subject matter of the present invention. So even if these three cited references (Kim et al., Brantl et al. and McQuinn) were combined, it is clear that the subject matter of amended claim 1 and claims 4 and 6 depending thereon, would not be suggested to the skilled person in the art.

(G) Referring to page 7 of the Office Action, the Examiner states that acrylates are polymers that are known to aid in absorption and thus fall within the "absorption promoting agent" category of claim 6. However, the Examiner has failed to provide any support for this statement. As noted in MPEP 2142, rejections on obviousness cannot be sustained with mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. The Examiner has not provided any underpinning to support the statement that acrylates are polymers that are known to aid in absorption.

(H) New claim 7 is the same as amended claim 1, except that it defines the drug layer in "consists of" language. Thus, the drug layer of claim 7 contains only the fentanyl or its salt, methyl vinyl ether-maleic anhydride copolymer, and at least one of hydroxypropyl cellulose, hydroxypropyl methylcellulose and hydroxyethyl cellulose. There can be no doubt that the drug

layer excludes the acrylate polymer which is a required component of the Kim et al. composition, and as indicated above, there is no suggestion in this reference which would lead one of ordinary skill in the art to exclude the acrylate polymer since to do so would result in a failure to achieve the object of Kim et al., namely, a stable and uniform hydrogel. For the same reason, neither of the secondary references, Brantl et al. or McQuinn, suggest omitting the acrylate polymer. For this reason alone, the subject matter of new claim 7 is clearly patentable over these three references, even if combined.

(I) Also on page 7 of the Office Action, in responding to Applicants' previous patentability arguments, the Examiner takes the position that Applicants' argument that the acrylate polymer is not contained in the drug layer was not persuasive since the instant claim language does not preclude the use of the acrylate polymer of Kim et al. The Examiner's argument clearly does not apply to new claim 7, since the "consists of" language does exclude the acrylate polymer.

(J) New claim 8 corresponds to amended claim 1, but like claim 6, recites that the drug layer also consists essentially of at least one member selected from the group consisting of a softening agent selected from glycerin and polyethylene glycol, an absorption promoting agent consisting of N-methyl-2-pyrrolidone and a sweetening agent. [In addition to the disclosure referred to above on page 7 of the specification in support of these particular softening and absorption promoting agents, Applicants note that these agents are used in Examples 1-9 in the specification.] There is no suggestion of this particular combination of components in the drug layer, in any of the references applied by the Examiner.

(K) For these reasons, Applicants take the position that the subject matter of claims 1, 4 and 6 is patentable over the applied references, as a result of which the rejection of these claims should be withdrawn. For the additional reasons given with respect to new claims 7 and 8, Applicants respectfully submit that these claims cannot be properly rejected based on these references.

The rejection of claim 2 under 35 U.S.C. §103(a) as being unpatentable over Kim et al. in view of Brantl et al. in view of McQuinn and further in view of Yamaguchi et al. (US '877), as well as the rejection of claim 3 under 35 U.S.C. §103(a) as being unpatentable over Kim et al. in view of Brantl et al. and McQuinn further in view of Miller, II et al. (US '551), and the rejection

of claim 5 under 35 U.S.C. §103(a) as being unpatentable over Kim et al. in view of Brantl et al., McQuinn, Yamaguchi et al. and Miller, II et al., are respectfully traversed.

The comments set forth above concerning the Kim et al., Brantl et al. and McQuinn references are equally applicable to all of these rejections, since claims 2, 3 and 5 are all directly or indirectly dependent on claim 1. Therefore, even if these other secondary references were combined with the other references, the result of such combination would still not suggest the subject matter of claims 2, 3 and 5.

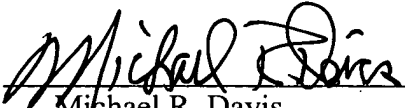
Therefore, in view of the foregoing amendments and remarks, it is submitted that each of the grounds of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Information Disclosure Statement

The Examiner is kindly reminded of the Third Information Disclosure Statement filed December 18, 2009, after issuance of the Office Action. Consideration of the IDS is requested.

Respectfully submitted,

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